

## Regiospecific and Stereoselective Syntheses of (±)-Reserpine and (–)-Reserpine

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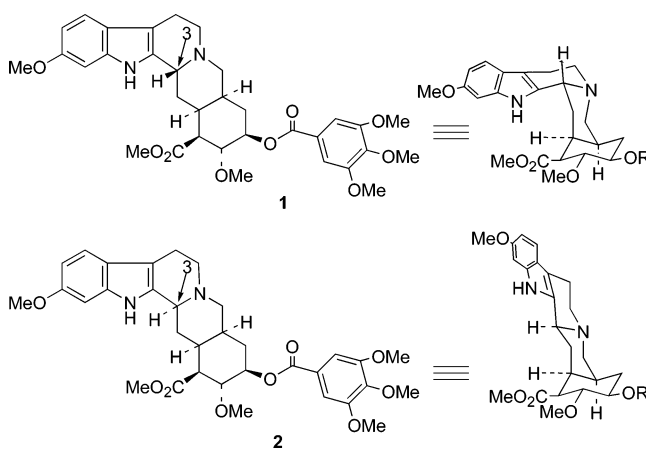
**Abstract:** Full details of three approaches to an entirely regio- and stereoselective synthesis of the well-known target reserpine are described, culminating in a total synthesis which efficiently meets these requirements.

### Introduction

Natural products of some complexity have played a major role in stimulating the design of new synthetic methods and in the evolution of the strategy and tactics of organic synthesis. For some chemists, the attractiveness of many of these substances as targets of synthesis is their bioactivity. For others, the structural challenge is the incentive to attempt their construction. For both reasons, almost half a century since its synthesis was first achieved,<sup>1</sup> the indole alkaloid reserpine (**1**) has been,<sup>2,3</sup> and will probably continue to be, a very attractive target to test novel approaches to its construction.

Imaginative and original as all these total syntheses of reserpine were, however, problems of regio- and stereochemistry still remained. In some syntheses, including the historic initial one,<sup>1a,4</sup> the C-3 center was initially produced regiospecifically but, exclusively or to a significant extent, as the epimer corresponding to isoreserpine (**2**). In others, the correct epimer

at C-3 was a major product, but it was accompanied by considerable quantities of an unwanted regioisomer.



Our plan for a regiospecific, as well as stereoselective, construction of reserpine was based on the anticipation that the kinetic closure of a regiospecifically produced iminium ion, **3**, would lead to the formation of the (desired) *less stable* arrangement at C-3 (vide infra). The requirement for regiospeci-

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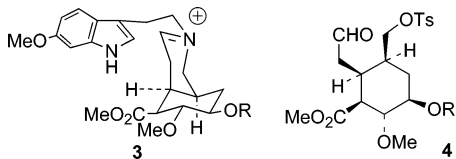
<sup>§</sup> Deceased Dec 28, 2004.

<sup>⊥</sup> Osaka Prefecture University.

- (1) (a) Woodward, R. B.; Bader, F. E.; Bickel, H.; Kierstead, R. W. *Tetrahedron* **1958**, *2*, 1. Woodward, R. B.; Bader, F. E.; Bickel, H.; Frey, A. J.; Kierstead, R. W. *J. Am. Chem. Soc.* **1956**, *78*, 2023; 2657. (b) For practical improvements, see: Novak, L.; Jilek, J. O.; Kakac, B.; Protiva, M. *Tetrahedron Lett.* **1959**, *5*, 10. Protiva, M.; Jilek, J. O.; Ernest, I.; Novak, L. *Tetrahedron Lett.* **1959**, *11*, 12.
- (2) (a) Pearlman, B. A. *J. Am. Chem. Soc.* **1979**, *101*, 6398; 6404. (b) Wender, P. A.; Schaus, J. M.; White, A. W. *J. Am. Chem. Soc.* **1980**, *102*, 6157; *Heterocycles* **1987**, *25*, 263. (c) Martin, S. F.; Grzejszczak, S.; Rüeger, H.; Williamson, S. A. *J. Am. Chem. Soc.* **1985**, *107*, 4072. Martin, S. F.; Rüeger, H.; Williamson, S. A.; Grzejszczak, S. *J. Am. Chem. Soc.* **1987**, *109*, 6124. (d) Gomez, A. M.; Lopez, J. C.; Fraser-Reid, B. *J. Org. Chem.* **1994**, *59*, 4048; **1995**, *60*, 3859. (e) Chu, C.-S.; Liao, C.-C.; Rao, P. D. *Chem. Commun.* **1996**, 1537. (f) Hanessian, S.; Pan, J. W.; Carnell, A.; Bouchard, H.; Lesage, L. *J. Org. Chem.* **1997**, *62*, 465. (g) Mehta, G.; Reddy, D. S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1399. (h) Sparks, S. M.; Shea, K. J. *Org. Lett.* **2001**, *3*, 2265. Sparks, S. M.; Gutierrez, A. J.; Shea, K. J. *J. Org. Chem.* **2003**, *68*, 5274.
- (3) For syntheses of the closely related deserpidine, see: (a) Szantay, C.; Blasko, G.; Honty, K.; Baitz-Gacz, E.; Tamas, J.; Töke, L. *Liebigs Ann. Chem.* **1983**, 1292. (b) Naito, T.; Hirata, Y.; Miyata, O.; Ninomiya, I.; Inoue, M.; Kamiuchi, K.; Doi, M. *Chem. Pharm. Bull.* **1989**, *37*, 901. (c) Baxter, E. W.; Labaree, D.; Ammon, H. L.; Mariano, P. S. *J. Am. Chem. Soc.* **1990**, *112*, 7682. Many routes to reserpine, although abandoned for one reason or another, deserve attention. Cf., inter alia, Isobe, M.; Fukami, N.; Nishikawa, T.; Goto, T. *Heterocycles* **1987**, *25*, 521.

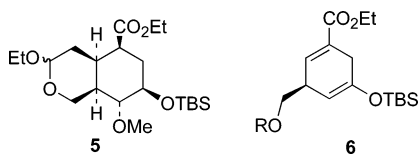
- (4) The original Woodward synthesis of reserpine goes through the initial formation of isoreserpine, its C-3 epimer, via a borohydride reduction in methanol which presumably involves axial addition of hydride to a *pre* chair iminium intermediate. A variety of modified reduction conditions of an iminium intermediate have been explored in the hope of producing reserpine directly, rather than via its C-3 epimer. Catalytic hydrogenation (cf. Gottfredsen, W. O.; Vangedal, S. *Acta Chem. Scand.* **1956**, *10*, 1414) also gives isoreserpine, but zinc–aqueous acid processes have been reported to yield reserpine selectively. (a) For instance, Weisenborn et al. (Weisenborn, F. L.; Diassi, P. A. *J. Am. Chem. Soc.* **1956**, *78*, 2022) reported the formation of reserpine, in unspecified yield, by zinc–aqueous acetic acid reduction. (b) Velluz et al. (Velluz, L.; Muller, G.; Joly, R.; Nominé, G.; Mathieu, J.; Allais, A.; Warnant, J.; Valls, J.; Bucourt, R.; Jolly, J. *Bull. Soc. Chim. Fr.* **1958**, 673) reported a 75% yield of reserpine, using zinc and aqueous perchloric acid on the 18-trimethoxybenzoate of the relevant iminium ion, and the same procedure, using the 18-acetate, was reported (Protiva, M.; Jilek, J. O.; Ernest, I.; Novak, L. *Tetrahedron Lett.* **1959**, *12*) to give a “3:1 mixture of reserpine to isoreserpine”. Martin (*J. Am. Chem. Soc.* **1987**, *109*, 6124) reports, however, that his group’s attempts to duplicate the favorable results reported earlier for these zinc–acid reductions gave, by contrast, ratios of 1:1.7–2.0 in favor of isoreserpine. See also: Wenkert, E.; Roychaudhuri, D. K. *J. Am. Chem. Soc.* **1958**, *80*, 1613.

ficity in the construction of such an iminium ion then led us to select **4** as our target. We now describe and compare three different approaches to the stereochemical problems embodied in **4**, and following a particularly successful regio- and stereospecific synthesis of that substance, we conclude this paper by examining the problems raised, and eventually solved, by the transformation of racemic and optically active **4** into ( $\pm$ )- and natural (-)-reserpine, respectively.<sup>5</sup>

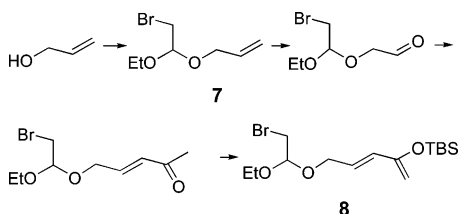


### Three Routes toward **4**

**(A) Stereocontrol via Radical Cyclization of a Bromoacetal.** The goal of the first route we now discuss was the bicyclic system shown in **5** in which the five contiguous asymmetric centers are properly placed for a potential transformation into target **4**. We believed that it should be possible to install these asymmetric centers with the required selectivity, by starting with a 5-substituted 3,6-dihydrobenzoic acid derivative, such as **6**, in the expectation that its lone asymmetric center would control the stereoselective introduction of the remaining four. We now describe how this scheme was reduced to practice.

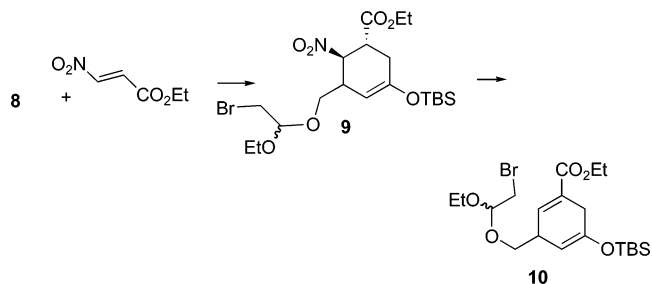


The structure of **6** formally suggests its construction via a 4 + 2 cycloaddition. The synthesis of a suitable diene for such a route was simply achieved by ozonolysis of the mixed bromoacetal **7**, derived from allyl alcohol, followed by Horner–Emmons condensation to the required unsaturated ketone. The desired diene **8** was readily formed from the latter by kinetic enolate formation<sup>6a</sup> and trapping with *tert*-butylchlorodimethylsilane.<sup>6b,c</sup>

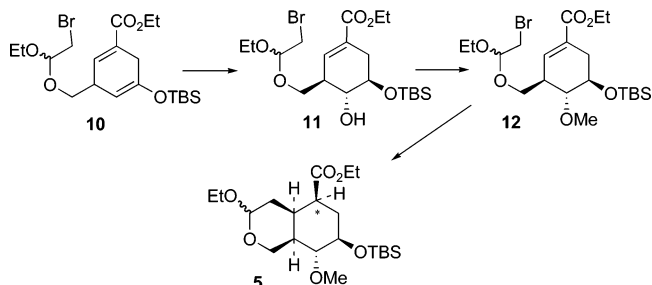


The mixed bromoacetal in these structures was intended to be more than a protecting group. It was also meant to serve as a crucial partner in the eventual radical cyclization planned to generate **5**. It was clear, of course, that the attractive formal possibility that target **6** might be reached by the 4 + 2 addition of diene **8** with methyl propiolate did not correspond to a real

possibility because of the incorrect regiochemistry anticipated from such a cycloaddition. The problem was simply solved by the use of ethyl 3-nitroacrylate, a stratagem which Danishefsky introduced to effect the overall reversal of propiolate cycloaddition regiochemistry.<sup>7</sup> In fact, the 4 + 2 cycloaddition of **8** with ethyl 3-nitroacrylate proceeded regiospecifically to give an *endo*–*exo* mixture of the crude adduct **9**, in essentially quantitative yield. Treatment of the mixture with 1 equiv of DBU,<sup>7</sup> at room temperature, then gave our desired intermediate **10**, in a satisfying 21% overall yield from allyl alcohol.



We considered two possibilities to achieve the stereoselective transformation of cyclohexadiene **10** to the bicyclic system **5**. Initial cyclization of the radical from the haloacetal chain in **10** was expected to be regioselective for the double bond conjugated with the ester, but attempting the reaction before the planned hydroboration of the enol silyl ether led to competitive abstraction of the doubly allylic hydrogen. The alternative sequence shown below, in which hydroboration of the electron-rich enol silane was performed before radical cyclization, should mitigate the problem and was, therefore, selected.



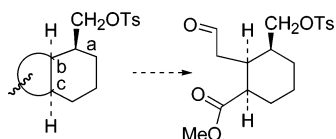
In the event, initial hydroboration of **10** was selective,<sup>8</sup> the expected result of the approach of diborane *anti* to the bromoacetal chain, and led to the correct arrangement of the three contiguous centers of **11**. Methylation of the secondary hydroxyl with methyl triflate, followed by radical cyclization of the resulting bromoacetal **12**, by tributylstannane in *tert*-butyl alcohol solution, then formed the anticipated *cis*-fused bicyclic system of **5**,<sup>9</sup> selectively forming the fourth asymmetric center in the process. We had expected that the fifth, and last, of the required asymmetric centers would be correctly established at the asterisked carbon of **5** in the termination step of the cyclization: transfer of a hydrogen atom should mainly take place from the more easily approached convex ( $\alpha$ ) side of the bicyclic system. The expectation turned out to be qualitatively

(5) The second and third reserpine syntheses described in detail in this paper have been outlined previously: (a) Stork, G.; Goodman, B. A. *Abstracts of Papers*, 192nd National Meeting of the American Chemical Society, Anaheim, CA; American Chemical Society: Washington, DC, 1986; ORGN 136. (b) Stork, G. *Pure Appl. Chem.* **1989**, *61*, 439.  
 (6) (a) Stork, G.; Kraus, G. A.; Garcia, G. A. *J. Org. Chem.* **1974**, *39*, 3459. (b) Stork, G.; Hudrlík, P. F. *J. Am. Chem. Soc.* **1968**, *90*, 4462. (c) Ireland, R. E.; Thompson, W. J. *J. Org. Chem.* **1979**, *44*, 3583.

(7) Danishefsky, S.; Hershenson, F. M. *J. Org. Chem.* **1979**, *44*, 1180.  
 (8) (a) Klein, J.; Levene, R.; Dunkelblum, E. *Tetrahedron Lett.* **1972**, 2845. (b) Kono, H.; Nagai, Y. *Org. Prep. Proced. Int.* **1974**, *6*, 1. (c) Larson, G. F.; Prieto, J. A. *Tetrahedron* **1983**, *39*, 855.  
 (9) Stork, G.; Mook, R., Jr.; Biller, S. A.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1983**, *105*, 3741.

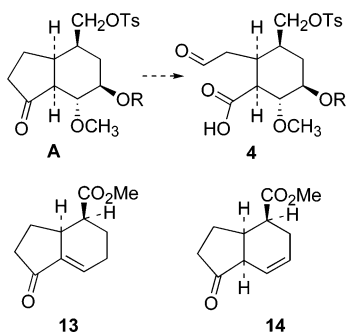
valid, but selectivity was only ~4.5:1 in favor of the required stereochemistry shown in **5**. It is, nevertheless, remarkable that **5** was obtained with a fair degree of stereoselectivity in only nine steps from allyl alcohol and in ~11% overall yield.

Various schemes were envisaged to improve the modest selectivity at the asterisked center of **5a** and to adjust oxidation states to convert **5a** into **4**, our ring E target. A route which would directly lead to the correct oxidation states of the aldehyde and carbomethoxy centers, via the cleavage sketched below, seemed less cumbersome and more attractive. This successful approach will now be described.

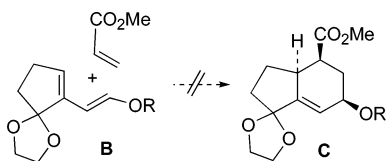


**(B) Stereocontrol via a *cis*-Hydrindane System.** The late intermediate **A**<sup>10</sup> was selected for this route to avoid the problems of the first scheme: regiocontrolled oxidative cleavage of the cyclopentanone ring would now directly produce the required carboxyl and acetaldehyde appendages of target **4**.

We initially considered some previously known hydrindenones, such as **13** and **14**,<sup>11a,b</sup> as possible intermediates toward **A**, but these were eventually abandoned because of low yields and selectivity problems.

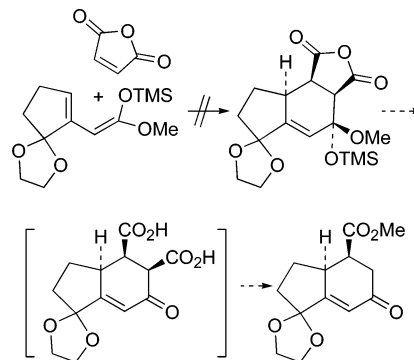


A related structure, such as **C**, would be an attractive target if it could be reached via the 4 + 2 cycloaddition shown in **B** to **C**, but that process would not lead to the desired regiochemistry.

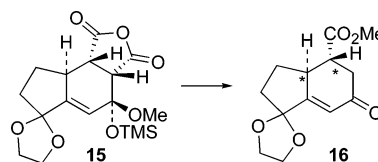


A simple solution to that regiochemistry problem suggested itself, however: use of maleic anhydride as the dienophile, together with a vinyl ketene acetal as the diene.<sup>12</sup> The required 3-carboxycyclohexenone system would then arise from the *endo* adduct shown below, by hydrolysis of the anhydride, ac-

companied by decarboxylation of the resulting  $\beta$ -ketoacid.<sup>13a,b</sup> The desired sequence is shown below:



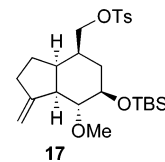
The sequence was successful, except for a crucial point: the major cycloadduct, obtained in 70% yield after 2 h in benzene, at room temperature, turned out to be the undesirable product of *exo* addition, **15**, mp 140–141 °C. The *exo* adduct structure was suspected on the basis of NMR determinations, including NOEs, and was confirmed by X-ray analysis. The result of its hydrolysis is then **16** with the *incorrect anti* relationship of the asterisked vicinal centers.<sup>14</sup>



This unanticipated result would not necessarily preclude the use of keto ester **16** on the route to reserpine, but the eventual epimerization that would be required at the ester center of **16** made this specific sequence less attractive than it originally appeared.

Despite this setback, the possibility that the *exo* addition leading to **15** might be an isolated case, and the intrinsic attraction of a vinyl ketene acetal–maleic anhydride route toward target **4**, encouraged us to carry out further studies on the stereochemistry of related cycloadditions.

Our earlier experience suggested that, in the construction of a target such as **A** (vide supra), the cyclopentanone carbonyl should be kept latent until the eventual cleavage of the five-membered ring. To avoid the possibility of  $\beta$ -elimination of the methoxyl, the generation of that carbonyl should involve neither base nor strong acid. The methylene indanone **17** appeared to be a precursor that would meet these requirements. We now describe its synthesis.

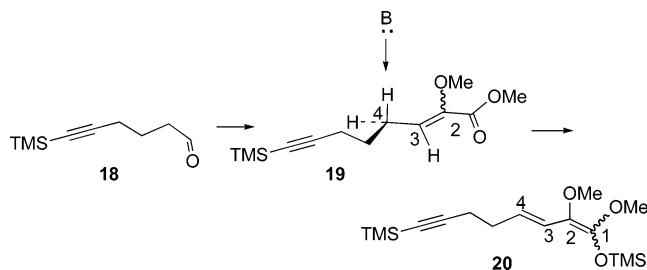


Condensation of trimethylsilylhexynal<sup>15</sup> (**18**) with the lithium enolate of methyl methoxyacetate, followed by in situ reaction

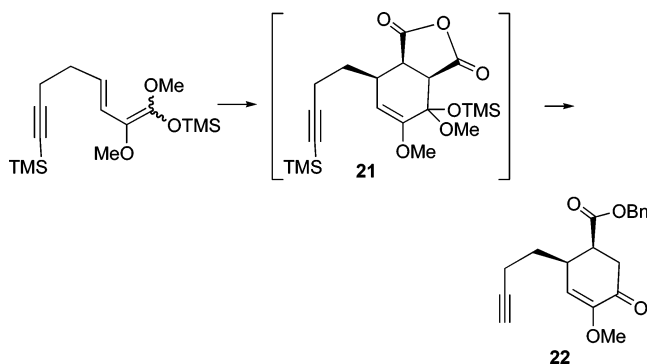
(10) The desirability of a target such as **A** has been pointed out previously: (a) Ficini, J.; Guingant, A.; d'Angelo, J.; Stork, G. *Tetrahedron Lett.* **1983**, 24, 907. (b) Jung, M. E.; Light, L. A. *J. Am. Chem. Soc.* **1984**, 106, 7614.  
 (11) (a) Roush, W. R.; Gillis, H. R.; Ko, A. I. *J. Am. Chem. Soc.* **1982**, 104, 2269. (b) d'Angelo, J.; Ortuño, R.-M.; Brault, J.-F.; Ficini, J.; Riche, C.; Bouchaudy, J.-F. *Tetrahedron Lett.* **1983**, 24, 1489.  
 (12) Grandmaison, J.-L.; Brassard, P. *Tetrahedron* **1977**, 33, 2047.

(13) (a) McElvain, S. M.; Morris, L. R. *J. Am. Chem. Soc.* **1952**, 74, 2657. (b) Lombardo, K. *Tetrahedron Lett.* **1985**, 26, 382.  
 (14) Livingston, D. A. Ph.D. Thesis, Columbia University; *Diss. Abstr. Int.*, **B** **1982**, 43 (5), 1496.

with benzenesulfonyl chloride and heating with DBU, gave the conjugated methoxy ester as a 5:1 mixture in favor of the desired (*Z*) isomer **19**. Separation was unnecessary because only the major isomer of the dienyl ketene acetals (cf. **20**) obtained by trapping the lithium enolates from **19** with chlorotrimethylsilane readily took part in the subsequent 4 + 2 cycloaddition. The required 3,4-*E* geometry of dienes **20** had been expected because deprotonation of their precursor should take place via the rotamer depicted in **19**, which avoids interference between one of the substituents at C-2 (be it methoxyl or carbomethoxy) and the alkyne chain at C4.<sup>16,17</sup>

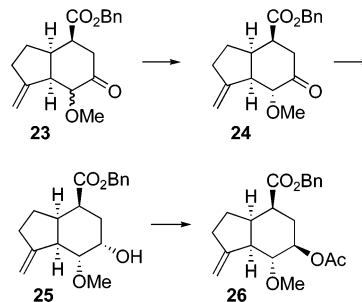


Maleic anhydride addition to the conjugated ketene acetals **20** gave a crude adduct, **21**, which, upon overnight reflux with aqueous THF, underwent release of the cyclohexenone carbonyl and hydrolysis–decarboxylation to the cyclohexenone carboxylic acid and finally was converted into its desilylated benzyl ester ethynylcyclohexenone **22**, the starting material for the planned radical cyclization, in about 50% overall yield from the ketene acetals **20**.



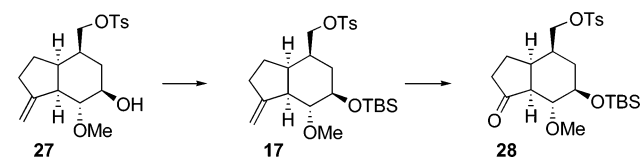
We expected a successful outcome of that cyclization. Earlier work from this laboratory had established that alkenyl radicals from addition of stannanes to acetylenes could be trapped intramolecularly by suitably situated double bonds.<sup>18</sup> In cyclohexenone **22**, however, the angle of approach of the alkenyl radical to the cyclohexene double bond might result in some interference with the carboxylic ester substituent. Conjugation of the ketone carbonyl with the double bond potentially involved in the desired vinyl radical addition should, on the other hand,

be favorable to the desired cyclization. In the event, treatment of **22** with tributylstannane in refluxing *tert*-butyl alcohol, followed by destannylation, led to the *cis*-fused methyleneindanone **23**. This was initially a mixture of methoxy epimers, but base-catalyzed equilibration gave the desired methoxyindanone **24**. This is as expected because the methoxy group is now not only equatorial but also on the less hindered convex side of the *cis*-indanone.

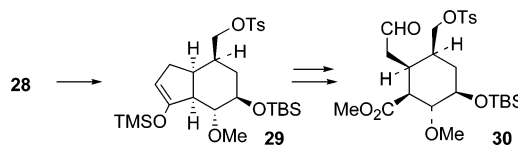


The cyclohexanone carbonyl of **24** was now transformed into the required  $\beta$  (equatorial) hydroxyl. That transformation, nontrivial because of the neighboring methoxy group, was effected by reduction of the cyclohexanone carbonyl of **24** with *L*-Selectride to the *axial* alcohol **25**, mp 106–107 °C, followed by clean inversion of its mesylate by displacement with cesium acetate,<sup>19,20</sup> thus producing **26** in 39% overall yield from **22**. The sequence completed the conversion of the starting aldehyde **18** to **26** in ~14% overall yield.

Reduction of **26** with lithium aluminum hydride to a diol, followed by tosylation of the primary hydroxyl, gave the crystalline tosylate **27**, mp 93–94 °C. Silylation to give **17**, mp 88–89 °C, and ozonolysis finally gave the desired intermediate, hydrindanone **28**, mp 99–101 °C, in essentially quantitative yield.



With the successful regio- and stereocontrolled synthesis of **28**, the five asymmetric centers of the reserpine E-ring had been correctly introduced and the system was ready for cleavage of the cyclopentanone ring. This was readily achieved by regio-controlled kinetic enolization–trapping<sup>6a-c</sup> to the trimethylsilyl enol ether **29**, which, following ozonolysis and treatment with diazomethane, gave our crucial intermediate, the aldehyde ester ( $\pm$ )-**30** (**4**, R = TBS), in 68% yield.



(15) Harris, G. D.; Herr, R. J.; Weinreb, S. M. *J. Org. Chem.* **1993**, *58*, 5452.

(16) For discussions of the deconjugation of some  $\alpha\beta$ -unsaturated esters, see: (a) Krebs, E.-P. *Helv. Chim. Acta* **1981**, *64*, 1023. (b) Kende, A. S.; Toder, B. H. *J. Org. Chem.* **1982**, *47*, 163. (c) Bell, S. H.; Cameron, D. W.; Feutrill, G. I.; Skelton, B. W.; White, A. H. *Tetrahedron Lett.* **1985**, *26*, 6519. (d) Cameron, D. W.; Looney, M. G.; Patterman, J. A. *Tetrahedron Lett.* **1995**, *41*, 7555. (e) Cameron, D. W.; Heisen, R. M. *Aust. J. Chem.* **2000**, *53*, 109. (f) Guha, S. K.; Shibayama, A.; Abe, D.; Ukaji, Y.; Inomata, K. *Chem. Lett.* **2003**, *32*, 778.

(17) For a discussion of the factors affecting the ratio of *E* to *Z* isomers from deprotonation–silylation of unconjugated esters, see: Ireland, R. E.; Wipf, P.; Armstrong, J. D., III. *J. Org. Chem.* **1991**, *56*, 650.

(18) Stork, G.; Mook, R., Jr. *J. Am. Chem. Soc.* **1987**, *109*, 2829.

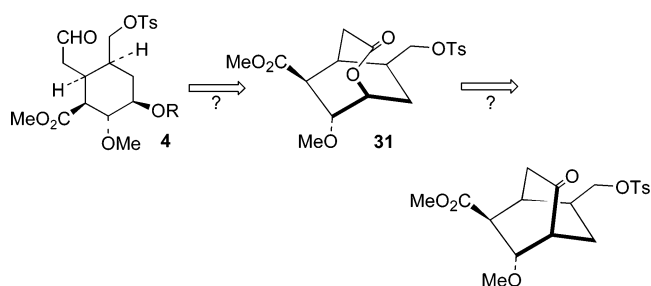
(19) Torisawa, Y.; Okabe, H.; Ikegami, S. *Chem. Lett.* **1984**, 1555.

(20) Wender et al. (Wender, P. A.; Schaus, J. M.; White, A. W. *Heterocycles* **1987**, *25*, 263) have described direct reduction of a closely related  $\alpha$ -methoxycyclohexanone to the epimer *trans* to the vicinal methoxy group, in the presence of ceric chloride (cf. also Rucker, G.; Horster, H.; Gajewski, W. *Synth. Commun.* **1980**, 623). We expect, but did not determine, that these conditions would be successful with **24**.

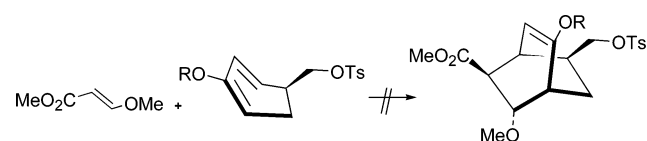


The synthesis of (±)-**30** just described was thus achieved in a relatively small number of steps and with a good level of stereocontrol, in an overall yield of ~9.2% from the starting aldehyde **18**. We were now in a position to examine the planned stereocontrolled conversion of **30** into reserpine, but before that final transformation is described, a further synthesis of **30** will now be described. It is noteworthy because it is regioselective, as well as stereospecific, and because it allows a particularly efficient construction not only of (±)-reserpine but also of natural (-)-reserpine.

**(C) Stereocontrol via a Bicyclo[2.2.2]octanone.** Bicyclic lactone **31** would obviously be an extremely attractive precursor of aldehydotosylate **30**. Reduction of its lactone system to the lactol stage should be possible without affecting the carbomethoxy group, thus releasing the acetaldehyde group and the cyclohexanol hydroxyl in the required 1,3-*cis* relationship shown in **30** (cf. **4**). The oxabicyclo[2.2.3]nonane system of **31** becomes especially appealing when viewed as the expected product of a Baeyer–Villiger oxidation of the related bicyclo[2.2.2]octanone, as indicated below:

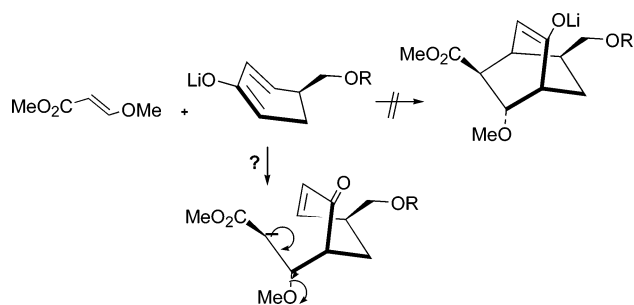


The scheme becomes even more attractive when the required bicyclooctanone is viewed as the product of a formal 4 + 2 cycloaddition, such as that shown here:

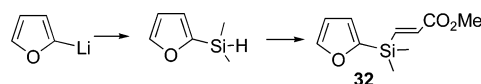


It was clear, however, that the mediocre reactivity of cyclohexadienes in Diels–Alder reactions, coupled with the very poor dienophilic properties expected of methyl 3-methoxyacrylate, would not allow this simplistic approach to the bicyclooctanone target.<sup>21</sup> One way to circumvent the problem of the low reactivity of cyclohexadienes could be to use what would be the operational equivalent of our contemplated Diels–Alder addition: a sequential double Michael reaction of the kinetic lithium enolate of an appropriate cyclohexenone with a suitable Michael acceptor.<sup>22a,b</sup> Unfortunately, methyl 3-methoxyacrylate proved unsuitable in the latter role. Quite possibly, the enolate intermediate in the intended cycloaddition underwent  $\beta$ -elimination of the methoxyl, rather than the desired intramolecular second Michael addition.<sup>23</sup>

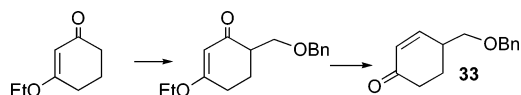
- (21) The considerably more reactive cyclopentadiene has been successfully added to methyl 3-methoxyacrylate under Lewis acid catalysis: Baldwin, S. W.; Tomesch, J. C. *J. Org. Chem.* **1974**, *39*, 2382.  
 (22) (a) Lee, R. A. *Tetrahedron Lett.* **1973**, 333. (b) White, K. B.; Reusch, W. *Tetrahedron* **1978**, *34*, 2439.  
 (23) A similar problem has been encountered with a 3-chloroacrylate; see ref 22b.



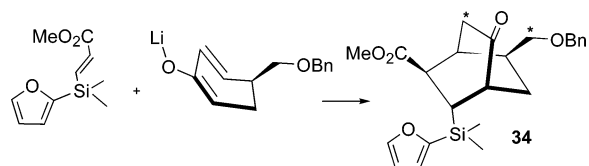
It was apparent that, for the approach to succeed, the acrylate acceptor would have to have a 3-substituent resistant to  $\beta$ -elimination, but later transformable to a methoxy group. A substituted silane was an obvious possibility.<sup>24a,b</sup> Methyl 3-(dimethyl-2-furylsilyl)acrylate (**32**) was selected as a molecule which should meet our requirements.<sup>25</sup> The desired silylacrylate was readily made, as shown below, from dimethyl-2-furylsilane (available by the reaction of chlorodimethylsilane with 2-furyllithium<sup>26</sup>) via the addition–metal hydride elimination it underwent with methyl acrylate, in the presence of dicobalt octacarbonyl.<sup>27</sup>



As the other partner in the planned double Michael reaction, we chose 4-(benzyloxymethyl)-2-cyclohexenone (**33**). Its synthesis had to avoid basic conditions,<sup>28</sup> a requirement met, *inter alia*, by our general method for the kinetic construction of 4-substituted cyclohexenones.<sup>29</sup> The process, sketched below, starting with the alkylation of the kinetic lithium enolate of 3-ethoxycyclohexenone with benzyloxymethyl chloride led us to (±)-**33**<sup>30</sup> in 68% overall yield.



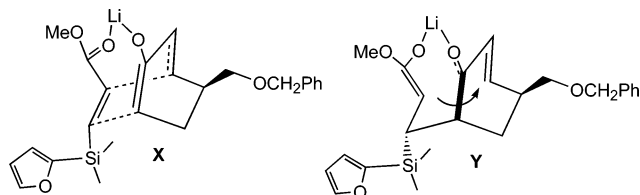
The crucial double Michael reaction proved remarkably effective: addition of the silyl acrylate **32** to a tetrahydrofuran solution of the kinetic lithium enolate of **33** gave, after a short time at 0 °C, the desired adduct **34**, as a single isomer, in 88% yield.



The stereochemistry shown for **34** had been expected. The single substituent on the cyclohexenone lithium enolate directed

- (24) (a) Tamao, K.; Kakui, T.; Akita, M.; Iwahara, T.; Kanatani, R.; Yoshida, I.; Kumada, M. *Tetrahedron* **1983**, *39*, 983. (b) Fleming, I.; Henning, R.; Plaut, H. *Chem. Commun.* **1984**, 29.  
 (25) The selection of a 2-furyl substituent on silicon was made in the expectation that it would facilitate later exchange for fluorine. Cf. Simas, A. B. C.; Stork, G. *J. Braz. Chem. Soc.* **1996**, *7*, 265.  
 (26) Barton, T. J.; Groh, B. L. *J. Am. Chem. Soc.* **1985**, *107*, 8297, footnote 3.  
 (27) See: Takeshita, K.; Seki, Y.; Kawamoto, K.; Murai, S.; Sonoda, N. *Chem. Commun.* **1983**, 1193.  
 (28) See, *inter alia*: MaGee, D. I.; Lee, M. L. *Synlett* **1997**, 786.  
 (29) Stork, G.; Danheiser, R. L. *J. Org. Chem.* **1973**, *38*, 1775.

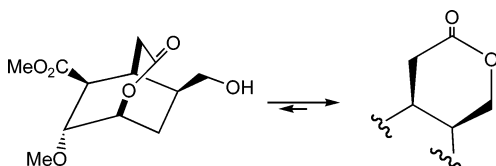
the acrylate acceptor to the opposite face of the cyclohexadiene ring. Further, the need to transfer the lithium cation from the ketone enolate to the ester carbonyl in the transition state for addition should favor their being held in proximity.<sup>31</sup>



It is worth noting that the same stereochemistry would result from viewing the reaction as an enolate-assisted *endo* 4 + 2 cycloaddition (cf. **X**), rather than as a two-step double Michael addition, as in **Y**. In any event, the observation of NOEs involving the asterisked hydrogens on **34** supported our hope that the lone asymmetric center of 4-benzyloxy-2-cyclohexenone had *stereospecifically generated, in one high-yield step, the 5-asymmetric centers of the eventual ring E of reserpine*.

This success was encouraging, but several transformations still had to be done to complete a route from **34** to lactone **31**, the penultimate intermediate before aldehyde ester **30**, or an analogue such as **4**, R = H: the benzyloxy group had to be changed into tosyloxy, the silyl substituent had to be replaced by a methoxyl, and the cyclic ketone had to become the required lactone.

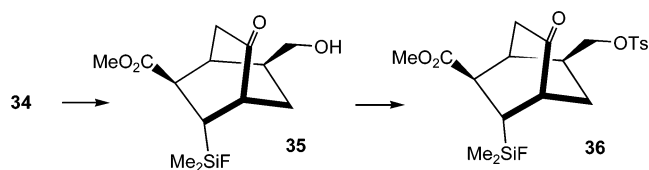
The order of these steps is not irrelevant. In particular, liberation and protection of the primary hydroxyl should precede Bayer–Villiger oxidation to lactone, to avoid the likely trans-lactonization shown below, as this would complicate further transformations to **30**.



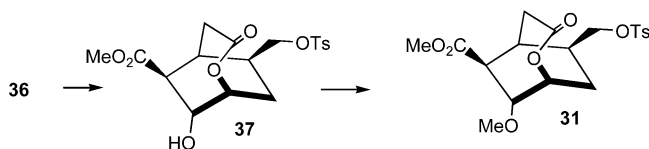
The simple solution was to postpone lactone formation until the benzyloxy group had been transformed to a tosyloxy substituent. Starting with **34**, the successful sequence began by replacing the furan ring on silicon by a fluorine, in preparation for the exchange of silicon for hydroxyl.

As we had hoped, simple treatment with tetrabutylammonium fluoride (TBAF) (2 min at room temperature) gave the desired fluorodimethylsilane in 88% yield. The stability of the silicon–fluorine bond to hydrogenolysis now allowed uneventful release of the primary alcohol (palladium/charcoal in ethyl acetate) to give **35**, which was tosylated to produce **36** in 64% overall yield from the bicyclooctanone **34**.

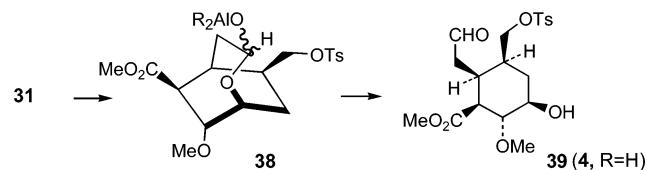
In agreement with the view that peracid-initiated exchange of silicon for oxygen is, mechanistically, similar to a Baeyer–Villiger oxidation, treatment of **36** with 2 equiv of *m*-chloroperbenzoic acid, in the presence of disodium hydrogen phosphate, gave lactone alcohol **37** in ~60% yield. There was



no evidence of any regioisomeric lactone, and it may be that the expected regioselectivity is enhanced by a silicon “ $\beta$  effect”<sup>32a,b</sup> which might be felt even in the presence of a silicon–fluorine bond. The lactone system of **37** conveniently served as a protecting group for one of the secondary hydroxyls, thus allowing methylation of the free secondary hydroxyl of **37** to give methoxylactone **31**, in almost quantitative yield, by reaction with methyl iodide in the presence of silver oxide.



It only remained to reduce **31** to a lactol to complete this route to **4**. This was accomplished with diisobutylalane in 84% yield. The process, as expected, proved selective for the lactone<sup>33a,b</sup> and took advantage of the fact that the rather strained bicyclic system was kept together, thanks to the strength of the oxygen–aluminum bond in product **38**,<sup>34</sup> thus protecting the latent aldehyde from reduction. Protic workup then allowed the system to relax to the free hydroxyaldehyde, completing the bicyclooctanone route to ( $\pm$ )-aldehyde ester **39** (**4**, R = H).



### Stereoselective Transformation of **4** to Reserpine

With the completion of two different stereoselective routes to **4** (R = H or TBS), we had reached the last, but crucial, challenge of joining that aldehydotosylate to 6-methoxytryptamine (**40**) to produce ring C with the correct C-3 configuration of reserpine. As illustrated at the beginning of this paper, we expected that goal to be reached via an iminium ion intermediate such as **3** (vide supra), via a *kinetic* nucleophilic “perpendicular-chair” addition<sup>35–37</sup> of the indole ring.

The crucial iminium ion **3** (vide supra) might conceivably be formed by intramolecular displacement of the primary tosylate of the imine resulting from the condensation of **4** with **40**. As it turned out, however, the pentacyclic system which

(30) For experimental details for this construction of ( $\pm$ )-**33**, see: Smith, A. B., III; Nolen, E. G.; Shirai, R.; Blasé, F. R.; Ohta, M.; Chida, N.; Hartz, R.; Fitch, D. M.; Clark, W. M.; Sprengeler, P. A. *J. Org. Chem.* **1995**, *60*, 7837.

(31) Cf. Ihara, M.; Toyota, M.; Abe, M.; Ishida, Y.; Fukumoto, K. *J. Chem. Soc., Perkin Trans 1* **1986**, 1543.

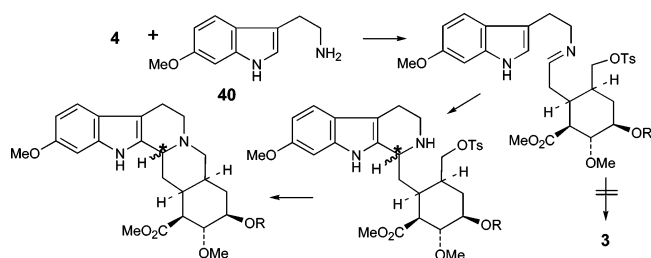
(32) (a) Hudrlík, P. F.; Hudrlík, A. M.; Nagendrappa, G.; Yimenu, T.; Zellers, E. T.; Chin, E. *J. Am. Chem. Soc.* **1980**, *102*, 6894. (b) Aida, T.; Asaoka, M.; Sonoda, S.; Takei, H. *Heterocycles* **1993**, *36*, 427.

(33) For examples of selective reductions of lactonic esters with DibalH, see: (a) Greenlee, W. J.; Woodward, R. B. *J. Am. Chem. Soc.* **1976**, *98*, 6075. (b) Sim, K. M.; Giuliano, R. M.; Fraser-Reid, B. *J. Org. Chem.* **1985**, *50*, 1774.

(34) The first published reference to the reduction of a lactone (five-membered) to a lactol by DibalH seems to be the following: Schmidlin, J.; Wettstein, A. *Helv. Chim. Acta* **1963**, *46*, 2799.

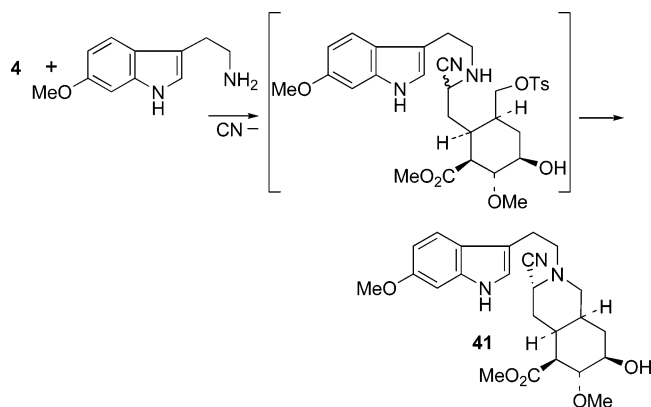
(35) The first observation of formation of the less stable epimer by addition of an indole ring to an intermediate iminium may be by van Tamelen in the course of his synthesis of yohimbine: van Tamelen, E. E.; Shamma, M.; Burgstahler, A. W.; Wolinsky, J.; Tamm, R.; Aldrich, P. E. *J. Am. Chem. Soc.* **1958**, *80*, 5006.

was obtained by the reaction of **4**, R = TBS, with **40** was a mixture of epimers at the C-3 center (asterisked). *In fact, the unwanted methyl iso-reserpate was the main product.*



We assumed that the unwelcome result implied that the sought-after iminium ion **3** had *not* been the intermediate in the formation of the reserpine–iso-reserpine mixture and that the imine intermediate from **4** and **40** had undergone faster cyclization with the indole, by a “Pictet–Spengler” reaction, than tosylate displacement to form the desired iminium ion **3**. We concluded that, to ensure that the required closure of ring D would occur before that of ring C, the imine intermediate would have to be trapped by an *external*, eventually removable, nucleophile, rather than intramolecularly by the indole ring. We decided to allow **39** and **40** to react in the presence of cyanide ion, in a Strecker reaction. Cyanide, which could be used in excess, if necessary, would be expected to compete successfully with the indole to form cyanopiperidine **41** or its epimer.

In the event, aminonitrile **41** was obtained, in 87% yield, by addition of 2 equiv of 6-methoxytryptamine to an acetonitrile mixture of aldehydotosylate **40** with excess potassium cyanide, in the presence of magnesium sulfate.



The crystalline aminonitrile **41** appeared to be a *single* isomer, with the newly introduced cyano group axial, as indicated.<sup>38,39,40a,b,c</sup>

In principle, the cyano group configuration was irrelevant since it was to be eliminated in the regeneration of iminium ion **3**,

(36) See, inter alia: (a) Wenkert, E.; Dave, K. G.; Haglid, F. *J. Am. Chem. Soc.* **1965**, *87*, 5461. (b) Gutzwiller, J.; Pizzolato, G.; Uskokovic, S. M. *J. Am. Chem. Soc.* **1971**, *93*, 5907. (c) Stork, G.; Guthikonda, R. *J. Am. Chem. Soc.* **1972**, *94*, 5109. See also footnote 33 of Martin's 1987 paper.<sup>2c</sup>

(37) For mechanistic rationalizations, see: (a) Toromanoff, E. *Bull. Soc. Chim. Fr.* **1966**, 3357. (b) Stevens, R. V. *Acc. Chem. Res.* **1984**, *17*, 289.

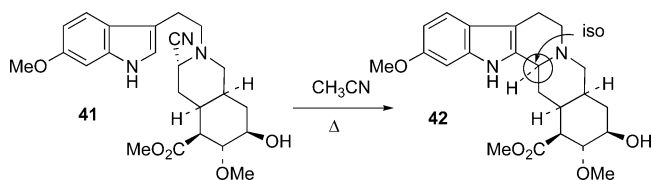
(38) The assignment of axial stereochemistry to the cyano group in **40** was supported by NMR data and by an X-ray structure determination of a related cyanopiperidine.

(39) Cyano compound **40** could be a *thermodynamic* product (we observed rapid exchange with <sup>15</sup>CN<sup>-</sup> in acetonitrile), so that kinetic arguments relating to the angle of initial entry (perpendicular chair) into the iminium ion intermediate may not be relevant to this case. Thermodynamic equilibrium is, in any case, also in favor of an axial cyano group in 2-cyanopiperidines, possibly because of an *endo anomeric* effect: cf. Booth, H.; Dixon, J. M.; Khedhair, K. A. *Tetrahedron* **1992**, *48*, 6161.

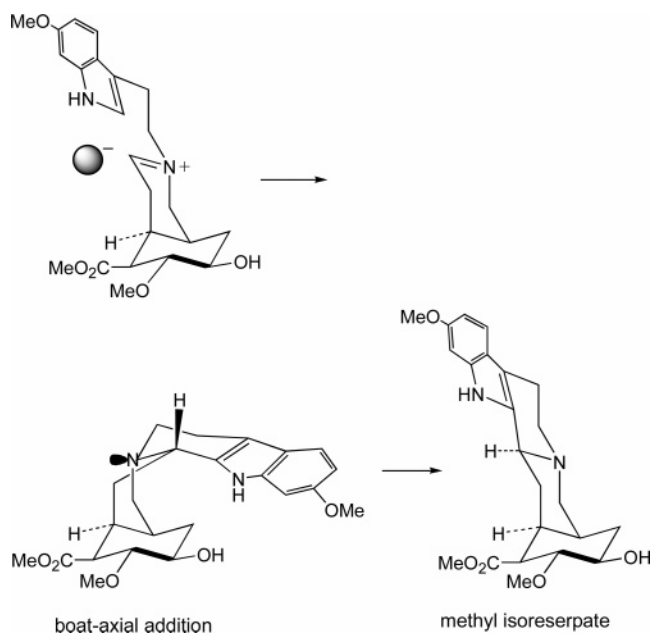
which we confidently expected would then form reserpine. As we discuss below, the goal was eventually reached, but the process turned out to be more complex than anticipated.

### Reserpine from Aminonitrile **41**

The desired elimination of cyanide from the *seco*-nitrile **41** was found to occur upon refluxing in acetonitrile, presumably leading to the derived iminium intermediate, since cyclization to a reserpine system *had* taken place. The product (~65% yield) proved again, however, to be *mainly* ( $\pm$ )-methyl iso-reserpate (**42**) rather than the ( $\pm$ )-methyl reserpate we had expected!



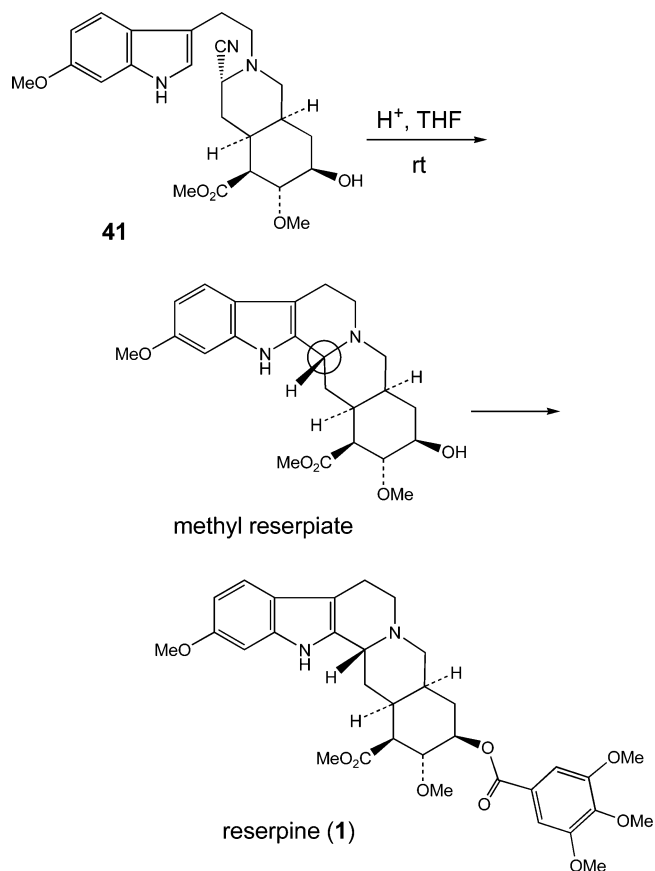
A rationalization of this disturbing turn of events eventually suggested a successful solution to the unexpected problem. The hypothesis that the iminium intermediate from **41** should lead to the desired (reserpine-like) axial attachment of the indole to the piperidine C-ring seemed unlikely to be incorrect. If so, the “free” iminium ion **3**, R = H, *might, again, not have been an intermediate* in the formation of the unwanted iso-reserpine stereochemistry at C-3. A fascinating possibility was that, under our experimental conditions, a tight ion pair between the iminium and cyanide ions was formed. If the cyano group in **41** is indeed axial, it might well block addition of the indole to the intermediate iminium ion in the “chair-axial” mode and lead instead to a “boat-axial” entry, as illustrated below. This, of course, would give, after boat to chair inversion, the unwanted chair-equatorial indole conformation of methyl iso-reserpate.



Simply avoiding the suspected tight ion pair intermediate, as by providing a possible escape for the cyanide ion, might finally

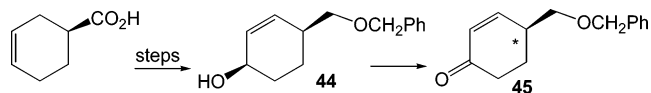
(40) See, inter alia: (a) Petrzilka, M.; Felix, D.; Eschenmoser, A. *Helv. Chim. Acta* **1973**, *56*, 2950. (b) Riedlicker, M.; Graf, W. *Helv. Chim. Acta* **1979**, *62*, 2053. (c) Bonon, M.; Chiaroni, A.; Riche, C.; Belocil, J.-C.; Grierson, D. S.; Husson, H.-P. *J. Org. Chem.* **1987**, *52*, 382.

lead to the free iminium ion (cf. **3**) which should now allow chair-axial addition and the correct C-3 stereochemistry. *In fact, treatment of 41, or its TBS ether, with a 10% solution of 1 N HCl in tetrahydrofuran, at room temperature, gave a ~90% yield of crystalline (±)-methyl reserpate, mp 238–239 °C, from*



which (±)-reserpine (cf. **1**), mp 256–258 °C (lit. mp 260.5–262 °C), was obtained by the usual acylation with 3,4,5-trimethoxybenzoyl chloride.

The construction of natural (–)-reserpine only required starting with the proper enantiomer of **33**. We found it convenient to make that substance, (4*S*)-4-(benzyloxymethyl)-2-cyclohexenone (**45**),  $[\alpha]_D^{26} -109.4$  ( $c = 3.58$ , methanol), by oxidation of the known cyclohexenol **44**,<sup>41</sup> itself readily available from (4*S*)-3-cyclohexenecarboxylic acid.<sup>42</sup>



Indeed, starting with **45**, duplication of the steps and conditions just described for the synthesis of (±)-reserpine now led to natural (–)-reserpine, mp 283–285 °C,  $[\alpha]_D^{24} -120.9$  ( $c = 0.642$ ,  $\text{CHCl}_3$ ) (lit.<sup>1a</sup> mp 286–288 °C,  $[\alpha]_D^{27} -118.9$  ( $c = 1.09$ ,  $\text{CHCl}_3$ )). The challenge of achieving regiospecific, as well as highly stereoselective, syntheses of (±)- as well as of natural (–)-reserpine had been met, in just 10 steps, from (±)-cyclohexenone **33** and from its enantiomer (–)-**45**, respectively.

**Acknowledgment.** This work was supported by grants from the National Institutes of Health and from the National Science Foundation.

**Supporting Information Available:** Experimental procedures and significant <sup>1</sup>H NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JA055744X

(41) Toyota, M.; Asoh, T.; Matsuura, M.; Fukumoto, K. *J. Org. Chem.* **1996**, *61*, 8687.

(42) Poll, T.; Sobczak, A.; Hartmann, H.; Helmchen, G. *Tetrahedron Lett.* **1985**, *26*, 3095.